

3449 10 JUL 27 P2:11



July 26, 2010

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Citizen Petition Regarding the Approval of Abbreviated New Drug
Applications for Vagifem® (estradiol vaginal tablets) 10 and 25mcg**

Dear Sir or Madam:

CITIZEN PETITION

Novo Nordisk Inc. ("Novo Nordisk") submits this Citizen Petition pursuant to the Federal Food, Drug, and Cosmetic Act ("FDC Act") and the Food and Drug Administration's ("FDA's" or "the Agency's") implementing regulations at 21 C.F.R. § 10.30 to request that the Agency require any Abbreviated New Drug Application ("ANDA") applicant for a generic version of 25 mcg Vagifem® (estradiol vaginal tablets) include in the labeling for the product information about the availability of and recommendation to begin treatment on the 10 mcg dosage strength of estradiol vaginal tablets. Novo Nordisk also asks that FDA refrain from receiving or approving

Novo Nordisk Inc.

Edward F. Hanover
Corporate Counsel
100 College Road, West
Princeton, New Jersey 08540
USA

Telephone:
609-987-5800
Fax:
609-987-5440

E-mail:
ehov@novonordisk.com
Internet:
www.novonordisk-us.com

FDA 2010.P.0403

CP

any ANDAs for 10 or 25 mcg generic versions of Vagifem® unless the applicant conducts well-controlled multiple endpoint clinical bioequivalence studies. Although Novo Nordisk does not know whether there is a pending ANDA for either or both strengths of a generic version of Vagifem®, Novo Nordisk submits this Citizen Petition in compliance with FDC Act § 505(q) in the event that such an ANDA exists.

Novo Nordisk acknowledges a Citizen Petition dated January 21, 2005, submitted to FDA by Warner Chilcott (Docket No. FDA-2005-P-0006) requesting that FDA require an ANDA for generic estradiol vaginal cream be supported by clinical study data. Novo Nordisk submitted a similar Citizen Petition dated February 18, 2009 (Docket No. FDA-2009-0089), requesting that FDA not approve any ANDA for a generic version of Vagifem® 25 mcg unless the generic applicant provides data from adequate and well-controlled multiple endpoint clinical trials designed to assess the decrease of vaginal pH, cytologic maturation of the vaginal epithelium and symptom relief. FDA has not issued a substantive response to either petition. Novo Nordisk adopts and reiterates many of the same arguments with regard to its request that FDA require that ANDA applicants demonstrate bioequivalence via clinical trials.

A. ACTION REQUESTED

Novo Nordisk asks that FDA not permit an applicant for 25 mcg generic Vagifem® to “carve out” language regarding the 10 mcg dosage strength. Specifically, Novo Nordisk asks that FDA require the following language in the labeling for a generic version of Vagifem®:

- “Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.” (Section 2:1 of Vagifem® Full Prescribing Information).

- “Generally, women should be started at the 10 mcg dosage strength.” (Section 2.2 of Vagifem® Full Prescribing Information).
- Information about Vagifem® 10 mcg that appears in sections 6.1, 11, 12.3, and 14.1 of the Vagifem® Full Prescribing Information as well as in the Highlights of Prescribing Information under the heading “Dosage Forms and Strengths.”

Novo Nordisk also asks that FDA refrain from approving 10 and 25 mcg ANDAs unless or until the applicant provides data from well-controlled multiple endpoint clinical trials. These trials should be conducted in line with FDA guidelines and should be sufficient to show that the drug is safe and effective and bioequivalent to the comparable dosage strength of Vagifem®.

B. STATEMENT OF GROUNDS

1. Vagifem® Background

FDA approved Vagifem® 25 mcg in March 1999 (NDA 20-908) for use by women for the relief of symptoms related to postmenopausal atrophic vaginitis due to estrogen deficiency.¹ Vagifem® 10 mcg (sNDA 013) was approved in November 2009 for the same indication. Both Vagifem® 10 and 25 mcg are 6 mm tablets administered intravaginally via a patented plastic applicator to provide local estrogen therapy. Once inserted, the tablet adheres to the vaginal wall and dissolves, providing a slow release of estradiol. The dissolved active ingredient then coats the vaginal walls, and is absorbed into the vagina where the estradiol binds to and activates estrogen receptors in the vagina, which promotes cellular maturation of the vaginal epithelium,

¹ Novo Nordisk announced on May 20, 2010, that it will discontinue the sale Vagifem® 25 mcg on July 30, 2010. Vagifem® 25 mcg will be sold through suppliers until supplies are exhausted. The expiration date of the final lots of Vagifem® 25 mcg will be approximately July 2013.

increases vaginal secretions and moisture, and normalizes the vaginal pH, all of which contribute to the resolution of the symptoms of vaginal atrophy.

When Vagifem® 25 mcg was first introduced, it was believed that 25 mcg was the necessary dosage for efficacy. However, studies conducted for the Vagifem® 25 mcg approval suggested that a 10 mcg dose might also be effective for women with postmenopausal atrophic vaginitis, so Novo Nordisk conducted a clinical trial to determine the efficacy of the 10 mcg dose. The trial showed that the 10 mcg dose is effective, and FDA approved the lower strength as well as new common labeling for both the 10 and 25 mcg dosage strengths.² The current labeling recommends that treatment begin with the 10 mcg dosage strength of Vagifem®, recommends that women start estrogen therapy at the lowest dose, and provides information on the clinical study used to establish the effectiveness of Vagifem® 10 mcg.

Novo Nordisk conducted 20 clinical trials, including 3 clinical pharmacology trials, 3 pharmacokinetic trials and 14 efficacy and safety trials, in the United States, Canada, Europe, and Australia, to support the approval of the Vagifem® products. For each trial, all of the subjects used Novo Nordisk's patented applicator to insert the tablet. Novo Nordisk currently has a method of use patent for Vagifem® 10 mcg for treatment of atrophic vaginitis due to menopause (U-1023).³

² The common labeling will be used until July 2013 when the last batch of the 25 mg strength expires. After July 2013, the labeling will only refer to the 10 mcg dosage strength.

³ U.S. patent 7,018,992, expires on Sept. 17, 2022.

2. Analysis

- a. FDA should not permit an ANDA applicant for generic Vagifem® 25 mcg to omit language recommending that women take the lowest available dose because doing so would render the drug less safe.**

FDA should require any ANDA applicant for generic Vagifem® 25 mcg to use the same labeling as used for Vagifem® 25 mcg and 10 mcg tablets. In particular, FDA should not permit an ANDA applicant to “carve out” the following language from the approved Vagifem® prescribing information:

- “Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.” (Section 2:1 of Vagifem® Full Prescribing Information).
- “Generally, women should be started at the 10 mcg dosage strength.” (Section 2.2 of Vagifem® Full Prescribing Information).
- Information about Vagifem® 10 mcg that appears in sections 6.1, 11, 12.3, and 14.1 of the Vagifem® Full Prescribing Information as well as in the Highlights of Prescribing Information under the heading “Dosage Forms and Strengths.”

FDA regulations permit approval of ANDA labeling that omits certain aspects of the listed drug’s approved labeling only if the “aspects of the listed drug’s labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.”⁴

⁴ 21 C.F.R. § 314.127(a)(7).

Novo Nordisk has a method of use patent and three-year Hatch-Waxman exclusivity for the use of Vagifem® 10 mcg for the treatment of atrophic vaginitis due to menopause. An ANDA applicant for a 25 mcg dosage strength product may seek to omit the above-mentioned language if the applicant does not seek approval for a 10 mcg dosage strength product. However, omitting this language would be contrary to the current recommended dosing approved by FDA for estradiol vaginal tablets as well as the dosing recommended by the medical community, and therefore could render the generic product less safe than Vagifem®.

Omitting information on the 10 mcg strength would also be contrary to FDA's own recommendations. FDA requires the labeling for hormone therapy products, including Vagifem®, to bear black box warnings related to the risks of estrogen and progestin therapy and recommendations that prescribers start patients on the lowest effective dose. FDA also published a draft guidance document for sponsors recommending that they “develop the lowest doses and exposures for both estrogens and progestins for indications sought” and “investigate dosing schedules and drug delivery systems that can achieve efficacy with the lowest possible exposure.”⁵ FDA uses its website to recommend to women directly that they should use estrogens and progestins “at the lowest doses for the shortest duration to reach treatment goals.”⁶

⁵ Draft Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommendations for Clinical Evaluation, January 2003, at 2 (“the Draft Guidance”).

⁶ See Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women (Updated), *available at* <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm>.

The current recommendations for women considering hormone therapy is that they should generally start treatment with the lowest dosage strength available. If information about dosing and the availability of a 10 mcg strength is omitted from generic labeling, some prescribers may not be aware that a lower dosage strength is available, potentially exposing some women to higher dosages of estradiol than necessary. In addition, some prescribers and patients may be misled into believing that the generic 25 mcg estradiol vaginal tablets is safer than the Vagifem® 25 mcg if the generic labeling does not recommend starting on a lower dosage. Thus, permitting an ANDA applicant to carve out language about the availability of the 10 mcg dosage strength as well as the recommendations that women generally begin treatment on the lowest dosage strength could have a negative impact on women's health and would render the generic product less safe than Vagifem®.

- b. FDA should not receive or approve an ANDA for generic versions of Vagifem® 25 mcg and 10 mcg unless the applicant demonstrates bioequivalence for both dosage strengths based on data from adequate and well-controlled multiple endpoint clinical trials.**

FDA should require that an ANDA applicant demonstrate bioequivalence by a well-controlled multiple-endpoint clinical trial. Under FDA's existing bioequivalence regulations, the types of evidence that an applicant may use to show bioequivalence, listed "in descending order of accuracy, sensitivity, and reproducibility," are: (1) *in vivo* tests in humans to measure the active ingredient, moiety, or metabolite in "whole blood, plasma, serum, or other appropriate biological fluid," or "[a]n *in vitro* test that has been correlated with and is predictive of bioavailability;" (2) an *in vivo* test in humans to measure urinary excretion of the active moiety or metabolite; (3) "[a]n *in vivo* test in humans in which an appropriate acute pharmacological effect of the active moiety" or active metabolite "are measured as a function of time;" (4) a well-

controlled clinical trial to “establish the safety and effectiveness of the drug;” (5) an “*in vitro* test acceptable to FDA;” and (6) “[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.”⁷

In vivo (and *in vitro*) tests in human blood, serum, or urine will not provide accurate or reliable data on bioequivalence for a generic Vagifem® product because Vagifem® acts locally within the vagina to treat atrophic vaginitis. The mechanism of action for locally-acting treatments for atrophic vaginitis means that typical routes of metabolism for estrogen are largely bypassed. The very low doses given locally assure that there is minimal systemic absorption of estradiol and concentrations of serum estradiol remain in the menopausal range, so the types of *in vivo* studies typically used to demonstrate the bioequivalence of systemically absorbed drug products are inadequate to demonstrate the bioequivalence of topical estradiol products. Therefore, an applicant seeking approval for a generic version of Vagifem® must demonstrate bioequivalence through an alternative scientifically valid method; namely, in a multiple endpoint clinical study designed to measure the safety and efficacy of the test drug in post-menopausal women with atrophic vaginitis. Efficacy should be measured by the decrease of vaginal pH, cytologic maturation of the vaginal epithelium and patient reports of symptom relief. Such a trial is the only meaningful type of safety and efficacy study that would meet the requirements of FDC Act §§ 505(j)(2)(A), 505(j)(8)(C), and 21 C.F.R. § 314.94(a).

In addition, FDA should require that any applicant seeking approval for a generic version of Vagifem® conduct a pharmacokinetic study designed as a parallel design bioequivalence study. A crucial aspect of such a study is the dissolution profile of the drug at varying pH levels. Novo Nordisk submitted 2 pharmacokinetic studies with its original NDA for Vagifem® 25 mcg

⁷ 21 C.F.R. § 320.24(b)(1)-(6).

and one pharmacokinetic study for Vagifem® 10 mcg, including a study of dissolution in a vaginal environment with a pH range of 3 to 6.8. These studies provided important information about dissolution and the range of pH is important because vaginal pH varies markedly in this population and decreases as treatment continues. Even though such a study is not, by itself, sufficient for ANDA approval, the pharmacokinetic qualities of estradiol tablets are crucial for the efficacy of the drug and therefore should be required for any generic version of Vagifem®.

Novo Nordisk also requests that FDA require that any applicant seeking approval of an ANDA for a generic version of a locally acting, topical estrogen therapy product conduct a clinical trial in accordance with the Agency's recommendations in the Draft Guidance. Although the Draft Guidance does not specifically address ANDAs, it is appropriate that an ANDA for estradiol vaginal tablets follow the document because of the unique challenges of showing bioequivalence for a locally acting, topical product. The Draft Guidance recommends that sponsors of a drug to treat vaginal atrophy complete at least one randomized, double-blind, 12-week, placebo-controlled clinical trial to support the efficacy of the drug. This should be the standard for a clinical trial to support the approval of a generic version of Vagifem®.

The Draft Guidance further recommends that only postmenopausal women be included in the study and that study participants be women "who have self-identified at least one moderate to severe symptom" of vaginal atrophy "that is bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0." Draft Guidance at 3. The co-primary endpoints that the draft guidance recommends for vaginal atrophy include mean change from baseline to week 12 of the symptom that is most bothersome to the subject, vaginal pH, and vaginal maturation index (parabasal, intermediate, and superficial cells). It is very important that

a generic version of Vagifem® meet these endpoints in order to assure that the generic product is effective for its intended use.

c. Conclusion

Novo Nordisk respectfully requests that FDA not approve any labeling for a generic Vagifem® product unless the labeling includes information on the 10 mcg strength and a recommendation that women generally begin treatment with the lowest dosage strength. The current recommendation on the use of estrogen and progestin therapy is that women should use the lowest effective dose available, so it is important that women have information about the availability of the 10 mcg dosage strength.

Novo Nordisk also requests that FDA not receive or approve any ANDAs for generic Vagifem® 10 mcg or 25 mcg without bioequivalence data from clinical trials because a clinical trial is the only reliable way to demonstrate bioequivalence for a locally-acting product like Vagifem®.

C. ENVIRONMENTAL IMPACT

A claim for categorical exclusion from the requirements for an Environmental Assessment is made under 21 C.F.R. § 25.31(a).

D. ECONOMIC IMPACT

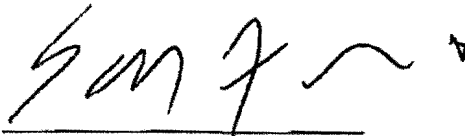
An economic impact statement will be submitted at the request of the Commissioner.

E. CERTIFICATION

Pursuant to FDC Act § 505(q), I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or

information which are unfavorable to the petition were disclosed to me. I further certify that I first became aware of the properties of Vagifem® when I first joined Novo Nordisk in January 2006 and also when the 10 mcg dosage strength was approved in November 2009, and I have not received nor do I expect to receive payments, including cash and other forms of consideration, to file this information or its contents, other than my normal compensation as a Novo Nordisk employee. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'E. Hanover', with a horizontal line underneath it.

Edward F. Hanover
Corporate Counsel
Novo Nordisk Inc.

cc: Keith Webber, Director
Office of Generic Drugs
CDER, FDA